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09/676,436	09/29/2000	Donna T. Ward	RTS-0169	5700

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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/676,436	Applicant(s) WARD ET AL.	
	Examiner Karen A. Lacourciere	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 2, 4-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

The amendment to claim 1, filed September 5, 2002, directs claims 1, 2, 4-10 and 12-15 to encompass an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 1 is directed to encompass antisense targeted to SEQ ID NO: 10 and SEQ ID NO: 11. As originally presented, the claims were drawn to antisense targeted to SEQ ID NO: 3. As amended, the claimed antisense, targeted to SEQ ID NO: 10 and 11, are considered to be unrelated to the originally presented invention, since each antisense to each target sequence claimed is structurally and functionally independent and distinct for the following reasons: each antisense sequence has a unique nucleotide sequence based on the target sequence, and the antisense targeted to the newly claimed sequences are to a different region of MEKK4, for example, the antisense targeted to SEQ ID NO: 10 and 11 includes exon sequences which do not exist in the originally examined SEQ ID NO: 3. Furthermore, a search of more than one (1) of the target sequences claimed in claim 1 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed target sequences. Therefore, the amended claims will only be examined to the extent that they read on the invention which was elected by original presentation, antisense targeted to a nucleic acid encoding MEKK4 wherein the nucleic acid is SEQ ID NO: 3.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for

prosecution on the merits. Accordingly, antisense targeted to SEQ ID NO: 10 and SEQ ID NO: 11 are withdrawn from consideration as being directed to a non-elected invention. Claims 1, 2, 4-10 and 12-15 will only be examined to the extent that they read on antisense targeted to SEQ ID NO: 3. See 37 CFR 1.142(b) and MPEP § 821.03.

A complete reply to the final rejection must include cancellation of nonelected subject matter or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

The rejection of record of claims 1, 2, 4-10 and 12-20 under 35 U.S.C. 112, second paragraph, set forth in the prior Office action (mailed 06-06-02) is withdrawn in response to Applicant's amendments filed September 5, 2002.

The rejection of record of claims 15-20 under 35 U.S.C. 112, first paragraph, set forth in the prior Office action (mailed 06-06-02) is withdrawn in response to Applicant's amendments filed September 5, 2002.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-10 and 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4-10 and 12-15 are considered to be indefinite because they read on non-elected subject matter, specifically, antisense targeted to SEQ ID NO: 10 and 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takekawa et al. (reference AC on PTO form 1449, filed 09-29-2000 and Genbank Accession Number AF002715) in view of Johnson (US Patent No. 5,981,265, referred to herein as '265, cited on PTO form 1449, filed 09-29-2000), Johnson (US Patent No. 6,312,934, referred to herein as '934), Johnson (US Patent No. 6,333,170, referred to herein as '170), Milner et al. (Nature Biotechnology, Vol. 15, pages 537-541, 1997) and Baracchini et al. (US Patent No. 5,801,154)

Claims 1, 2 and 4-15 are drawn to compounds 8 to 50 nucleobases in length that specifically hybridize to a coding region of a nucleic acid encoding MEKK4 (SEQ ID NO:

3) and inhibits the expression of MEKK4. Further limitations include wherein the antisense comprises modified bases, including 5-methylcytosine modifications; modified sugars, including 2'-O-methoxyethyl modifications; internucleoside linkage modifications, including phosphorothioate; chimeric antisense, and compositions comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system. The claims are further drawn to methods to inhibit the expression of MEKK4 in cells *in vitro* using the claimed antisense molecules.

Takekawa et al. teach the full length sequence of MTK1 (see page 4980, second column, fourth paragraph, and Genbank Accession number AF002715), which is the same sequence as SEQ ID NO: 3 of the instant application and includes the coding region, and teach that MTK1 is a human mitogen-activated protein kinase kinase kinase, and likely to be the human homologue of MEKK4 (see for example, page 4980, first column). Takekawa et al. do not teach antisense targeted to the coding region of SEQ ID NO: 3 or inhibiting the expression of MTK1 (MEKK4) in cells using antisense, nor do they teach the modifications claimed.

'265, '934, and '170 each teach making antisense targeted to nucleic acids encoding MEKK proteins, including MEKK4, however, none of these patents teach SEQ ID NO: 3. '265 (see for example columns 15-16) teaches making antisense targeted to nucleic acids encoding MEKK proteins and provides examples of nucleic acids encoding mouse MEKK proteins, including mouse MEKK4. '934 teaches making antisense targeted to nucleic acids encoding MEKK proteins, particularly the human versions of MEKK proteins (see for example, columns 14-15) and specifically teaches

targeting said antisense to the coding region (see for example, column 14, lines 19 to 25) and teaches making modifications to that antisense, including base modifications and backbone modifications, such as phosphorothioate, and teaches a length for antisense in the range of 15 to 50 nucleotides long (see for example col. 14, lines 50-52 of '934). '170 teaches making antisense targeted to nucleic acids encoding MEKK proteins (see for example columns 27 to 29) and provides examples of nucleic acids encoding mouse MEKK proteins, including MEKK4 splice variants, and teach modifying antisense for nuclease stability, including phosphorothioate modifications (see for example column 28. '170 teaches that antisense targeted to nucleic acids encoding MEKK can be used to investigate the role of MEKK in disease states as well as the normal cellular function of MEKK in healthy tissue and can be used in this capacity in cell culture (see '170, column 28 line 63 to column 29, line2).

Milner et al. teach methods of making and screening antisense molecules against a desired target gene in any region of the gene, including the coding region.

Baracchini et al. teach 2'-O-methoxyethyl sugar modifications, 5-methyl cytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity and teach antisense oligonucleotides of 8-30 nucleotides in length (see for example columns 6-9). Baracchini et al. teach targeting antisense to the coding region of a target gene. Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to make an antisense molecule targeted to a nucleic acid encoding MEKK4 (SEQ ID NO: 3), based on the sequence taught by Takekawa et al., because '265, '934, and '170 each teach making antisense targeted to nucleic acids encoding MEKK proteins, including MEKK4, and Takekawa et al. teach that their nucleic acid encodes the human homologue of MEKK4 and is involved in the same signaling pathway in humans as the proteins disclosed by '265, '934 and '170. It would have been obvious to target said antisense to the coding region of a nucleic acid encoding MEKK4 of SEQ ID NO:3 because it was conventional in the art to target the coding region with antisense, as exemplified by Baracchini et al., and because '934 specifically contemplates targeting the coding region of a nucleic acid encoding MEKK4. Methods of making antisense targeted to a known gene, including antisense targeting the coding region, were well known in the art at the time the instant invention was made, as exemplified by Milner et al. It further would have been obvious to make such antisense of a length within the range of 8-50 nucleobases (as taught by Baracchini et al. and '170), because antisense of a short length are more easily synthesized and easier to deliver to cells and '170 explicitly teaches antisense within this range (15-50 nucleotides) for targeting nucleic acids encoding MEKK proteins. It would have been further obvious to make said antisense comprising modifications, including 2'-O-methoxyethyl, 5-methyl cytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, as taught by Baracchini et al., because such modifications were routine and well known in the art as modifications which

enhance the stability, uptake and affinity of an antisense molecule (see for example Baracchini et al. column 6, paragraph 3) and because both '170 and '934 teach modifying antisense targeted to MEKK nucleic acids. It would have been obvious to one of ordinary skill in the art to make a composition comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al.

One of ordinary skill in the art would have been motivated to make antisense targeted to the coding region of a nucleic acid encoding MEKK4 of SEQ ID NO: 3, because '265, '934 and '170 each teach targeting nucleic acids encoding MEKK proteins, including MEKK4 ('265 and ' 170) and human MEKK proteins ('934), using antisense and '934 specifically teaches making said antisense to target the coding region of a nucleic acid encoding human MEKK4 and Takekawa et al. teaches that SEQ ID NO: 3 encodes a human MEKK4 homologue. Antisense was well known in the art as a means to selectively inhibit the expression of a gene and '170 and '934 particularly teach using antisense targeted to nucleic acids encoding MEKK proteins, including antisense targeted to a coding region in '934, as a means to study the cellular function of MEKK proteins. Takekawa et al. teach that the role of MTK1 (SEQ ID NO:3) is not fully understood (see for example, discussion section) and one of ordinary skill in the art would have been motivated to make antisense to MEKK4 (SEQ ID NO: 3) to use *in vitro*

in order to study the role of MTK1 (MEKK4, SEQ ID NO:3) in cells. One of ordinary skill in the art would have been motivated to make such antisense within the range of 8-50 nucleotides in length and with the modifications and in the compositions taught by Baracchini et al. for the benefits of ease of synthesis and delivery and to realize the benefits of improved stability and hybridization properties these modifications provided.

One skilled in the art would have expected to be able to find antisense which targets the coding region of a nucleic acid encoding MEKK4 and inhibits the expression of MEKK4 (SEQ ID NO:3), because the sequence of the coding region of a nucleic acid encoding MEKK4 (SEQ ID NO: 3) was known in the art and methods of screening for antisense to a known gene were routine (see for example Milner et al.) and the skilled artisan would have expected to find inhibitory antisense within the coding region because it is very large.

It would have been obvious to one of ordinary skill in the art to use antisense targeted to the coding region of a nucleic acid encoding MEKK4 in a method of inhibiting the expression of MEKK4 (SEQ ID NO: 3) in cells *in vitro* (cell culture), because it would be an obvious use for an antisense molecule designed to hybridize to and inhibit the expression of a nucleic acid encoding MEKK4 (SEQ ID NO:3) and '170 and '934 both teach using antisense targeted to nucleic acids encoding MEKK proteins in cells in culture as a means to study cellular function.

Therefore, at the time the instant invention was made, the invention of claims 1, 2 and 4-15, as a whole, would have been obvious to one of ordinary skill in the art.

Response to Arguments

Applicant's arguments filed September 5, 2002 have been fully considered but they are not persuasive. In response to the rejection of record of claims 1, 2 and 4-15 under 35 USC 103(a), set forth in the prior Office action (mailed 06-06-02). These arguments have been considered to the extent that they read on the rejection of claims 1, 2, 4-10 and 12-15 under 35 USC 103(a), set forth herein.

Applicant argues that the amendments to the claims filed September 5, 2002 have overcome the rejection of record because the claims now recite specific regions of the target nucleic acid. Applicant argues that only with the teaching of the instant specification would the skilled artisan understand that particular regions of the MEKK4 gene would be successful targets for antisense compounds. Applicant argues that the regional limitation is not taught in the prior art and further that there is no suggestion to combine the teachings of the cited references.

These arguments have not been found to be persuasive because Applicant has amended the claims to target one particular region of SEQ ID NO:3, the coding region, and the prior art specifically teaches targeting the coding region of a nucleic acid encoding MEKK4 (see the '934 patent) and the sequence of the coding region of SEQ ID NO:3 was known in the art (see the Takekawa et al. reference). Further, the cited prior art references do provide a suggestion to combine the cited references, as discussed in the rejection of record set forth herein. For example, each of the references '265, '934 and '170 teach targeting nucleic acids encoding MEKK proteins,

including MEKK4 ('265 and ' 170) and human MEKK proteins ('934), using antisense, and '934 specifically teaches making said antisense to target the coding region of a nucleic acid encoding human MEKK4 and Takekawa et al. teaches that SEQ ID NO: 3 encodes a human MEKK4 homologue.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
November 15, 2002

SEAN McGARRY
PRIMARY EXAMINER